SECTION III
REMARKS

Regarding the Amendments

By the present Amendment, claims 1, 3, 4, 7, and 8 have been amended as set forth in the above Complete Listing of the Claims. The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application.

New claims 20-29 have been added.

As provided, all claims in the above Complete Listing of the Claims are supported by the specification and the original claims. No new matter has been added, as defined by 35 U.S.C. § 132.

By the present amendment, cancellation of claims 5, 6, 9, 16, and 17 is requested, without prejudice.

It is noted that a preliminary amendment was submitted on July 22, 2004, concurrent with the original filing of the application, amending claims 4, 9, 10, 13-16 and adding new claims 17-19. However both the Office Action requiring restriction mailed December 13, 2006 and the Office Action mailed April 2, 2007 indicate that the pending claims are 1-16. In fact, the pending claims should be listed as claims 1-19. The above Complete Listing of the Claims includes previously added claims 17-19 and presently added claims 20-29.

Thus, upon entry of the amendments, claims 1-4, 7, 8, 10-15, and 18-29 will be pending.

Notice to Comply with Sequence Requirements

The examiner notes that the application fails to comply with the sequence requirements of 37 C.F.R. § 1.821 by failing to include sequence identifiers of sequences in the text of the specification or in the claims. By the present amendment the specification and claims have been amended to include sequence identifiers throughout the specification and claims, where required. Specifically, sequence identifiers have been added to the paragraphs of the specification at page 4, paragraph 4 and at pages 5-6, the paragraph bridging those pages. Additionally, sequence

identifiers have been added to claims 3 and 8 and are present in the new claims, as required. As such, the application is in accordance with the requirements of 37 C.F.R. § 1.821

Claim Objection

Claim 9 is objected to because of the use of the abbreviations Gd, Fe or F in the text of that claim. By the present amendment claim 9 has been cancelled. Accordingly the objection of claim 9 is moot. Withdrawal of the objection is respectfully requested.

Rejection of Claim 16 Under 35 U.S.C. §112, Second Paragraph

The examiner has rejected claim 16 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. By the present amendment claim 16 has been cancelled. Accordingly the objection of claim 16 is moot. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-16 Under 35 U.S.C. §112, First Paragraph, Written Description

The examiner has rejected claims 1-16 as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. In general, the examiner has stated that the claims "encompass a genus of unspecified i) transmembrane modules, ii) address modules, and iii) signaling modules." (Office Action mailed April 2, 2007, page 6.) Applicants respectfully disagree.

Claim 1, as amended, specifically recites the structure of the claimed conjugate as:

transmembrane module-address module-signalling module

Furthermore, amended claim 1 contains language describing the functional characteristics of each of the transmembrane modules, address modules, and signaling modules contained within the conjugate of the claim. In the claimed conjugate, the transmembrane module is specified as a transport peptide capable of penetrating the plasma membrane, the address module is specified as a peptide nucleic acid (PNA) which hybridizes with a mRNA, the expression or mis-expression of which is associated with a tumor disease and the signaling module is specified as being selected from the group consisting of Gadolinium, iron and fluorine. Addition of such language is fully

is fully supported by the specification and claims as originally filed. Specifically, support for the language regarding the transmembrane modules may be found at page 4, second full paragraph. Support for the language regarding the address modules may be found at page 5, second full paragraph. Support for the language regarding the signaling modules may be found in the language of original claim 9 (now cancelled).

Regarding the language "transmembrane module (TPU)" the claimed subject-matter has been limited to "transport peptides capable of penetrating the plasma membrane." Peptides which translocate over the plasma membrane in an energy and endocytotic independent manner were well known at the filing date of the application. For example, in the specification on page 4, in the second full paragraph, reference is made to Derossi et al. (1998) and Pooga et al. (1998) in which such kind of peptides are reviewed. Both references were cited in the IDS filed September 29, 2004, as References AH and AG, respectively. Moreover, both references report that such peptides are capable of internalizing macromolecules into cells. Further, Derossi et al. discuss which domain and residues are necessary for the translocation properties (e.g. page 84, right column), discuss variants and refer to other polypeptides, such as signal sequences, which have been shown to be internalized into a cell according a similar mechanism (e.g. page 86, last paragraph). As such transport peptides and their mechanism of translocation were well recognized at the filing date of the application, the phrase "transport peptides which can penetrate the plasma membrane" sufficiently specifies the claimed transport peptides, because a skilled person at the time of filing of the invention would have immediately envisioned which kind of peptides are encompassed by the claim.

Regarding the language "address module" the specification refers to PNAs which hybridize with a mRNA, the expression or mis-expression of which is associated with a tumor disease, and the specification lists some exemplary tumor genes for targets (page 5, last full paragraph). At the filing date it was known that PNA is a nucleic acid analog which hybridizes to a complementary mRNA according to the Watson-Crick base pairing rules. Further, it was known that PNA oligomers show a strong antisense effect in cells and that PNA, as well as antisense applications of PNAs, were reported at the filing date of the application. As the binding mechanism of PNAs to mRNA was known, the functional phrase "hybridizes with a mRNA the expression or mis-expression is associated with a tumor disease" sufficiently defines the claimed PNA, because respective target sequences of tumor genes were known in the art and a PNA having the

complementary sequence thereto can be easily obtained by solid phase peptide synthesis as shown in Example 1 (C) of the specification.

Regarding the language "signalling module" the claims have been limited to the three signalling modules specified in the specification by amendment of claim 1.

As outlined above, transport peptides as well as antisense PNAs capable of hybridizing to mRNA target sequences of tumor genes were well recognized in the art at the filing date. Additionally, as described above, the specification and claim language provides description of both structural and functional characteristics of the conjugate of independent claim 1 and its component parts. Therefore, it is concluded that the claims as amended satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Though the examiner has only rejected claims 1-16, it is noted that claims 1-19 were pending at the time of the present Office Action. The above arguments are equally applicable to the subject matter of claims 17-19 and newly added claims 20-29. As such, it is respectfully submitted that all of the presently pending claims 1-4, 7, 8, 10-15, and 18-29 are in compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. Removal of the rejection of claims 1-16 is therefore respectfully requested.

Rejection of Claims 1-16 Under 35 U.S.C. §112, First Paragraph, Enablement

The Examiner has also rejected claims 1-16 as lacking enablement, alleging that the specification does not provide an enabling disclosure for a diagnostic conjugate as broadly claimed. Applicants respectfully disagree.

In discussing the alleged lack of enablement of the conjugate, the examiner specifically discusses each of the component parts of the conjugate, the transmembrane module, the address module and the signaling module. Applicants submit that one of skill in the art would have been enabled at the time of filing of the present invention to make and use the claimed conjugates comprising the recited component parts.

Regarding use of transport peptide as a "transmembrane module," while the examiner cites that the specification provides only SEQ ID NOs 2, 3, and 4 as examples, it is submitted that additional peptides which translocate over the plasma membrane in an energy and endocytotic independent manner were well known at the filing date of the application. As set forth above, the Derossi et al. (AH) and Pooga et al. (AG) references review such types of peptides and report that such peptides are capable of internalizing macromolecules into cells. Further, Derossi et al. discuss necessary domain and residues for translocation properties, discuss variants and refer to other polypeptides. As such, peptides as defined in claim 1 were readily available in the art at the filing date of the application.

Further, it had been reported that these peptides can transport PNA oligomers across the cell membrane (see e.g. Braun et al.). Hence, it would have been predictable to one of skill in the art at the time of filing of the present application that that the claimed conjugates comprising a transmembrane module would be functional for any transport peptide capable of penetrating the plasma membrane. It would not have required undue experimentation to identify other transport peptides than SEQ ID NOs. 2, 3 and 4 with such properties, because these types of peptides were well recognized in the art (see, e.g. Pooga et al. or Derossi et al., whereas Derossi et al. further refers to additional polypeptides having internalizing sequences). Domains and regions of these peptides which are important for the transmembrane activity as well as variants thereof were reported in the art (see e.g. Derossi et al. or Pooga et al.) As the amino acid sequences of these peptides were described in the prior art, the peptides can be obtained by solid phase peptide synthesis as shown in the working example of the specification without undue burden.

Regarding the protein nucleic acids (PNA) component of the claimed conjugate of independent claim 1, it was known in the art that these nucleic acid analogs hybridize to a complementary mRNA target sequence according to the Watson-Crick base pairing rules. Hence, there was, at th4e time of filing of the present application, a clear and known relationship between the mRNA target sequence and the structure of the claimed PNA which was understood and predictable, because a number of antisense studies with PNAs were reported prior to the filing date of the application. Therefore, a skilled person could have made the claimed PNA without undue burden, once a mRNA target sequence had been identified, by synthesizing a PNA oligomer having the complementary sequence to the mRNA target sequence, for example, by a solid phase synthesis as shown in the working example of the application. The mRNA target sequence can be taken from

be taken from the tumor gene to be detected. Genes, expression or mis-expression of which is associated with a tumor disease, and their sequences are readily available from the art (see e.g. Schiavone et al., pages 779 and 780). Thus, a mRNA target sequence for the claimed PNA of the diagnostic conjugate could have been obtained by one of skill in the art as of the time of filing without undue burden. Moreover, because most of the genes, expression or mis-expression of which is associated with a tumor disease were already targets of antisense studies, suitable sequences for antisense oligomers against these genes were readily available (see Schiavone et al., pages 779 and 780). Therefore, it would not have required undue experimentation or a burden to identify an antisense sequence to a mRNA of a gene, expression or mis-expression of which is associated with a tumor disease, and to make a PNA according to the claimed invention. Further, it was known that a PNA oligomer complementary to a mRNA target sequence will hybridize thereto.

In the conjugate of claim 1, the PNA is only required to recognize and anneal to the mRNA target sequence; contrary to an antisense therapy it is not necessary that the PNA switch-off or modify expression of the target gene. Schiavone et al., cited by the Examiner, report that antisense applications with oncogenes have been extensively studied: "*a wide number of oncogenes have been then successfully targeted with antisense oligos either in vitro or in vivo*" (page 779, 1st column, 4th paragraph at the bottom). Hence, Schiavone et al. confirm that a large number of antisense oligos, i.e. antisense sequences, were readily available against genes whose expression or mis-expression is associated with a tumor disease. Therefore, a skilled person could have selected from these antisense sequences to make a PNA according to the invention without any undue burden.

In relation to the signalling module, the claimed Gadolinium, iron and fluorine were known to be used in tumor imaging as of the time of filing of the present application. Therefore, it is predictable that the claimed invention would have been enabled using these signalling modules as a part of the structure of the claimed conjugate. Methods for linking these signalling modules to peptide-conjugate were known. Thus, a skilled person could have made the claimed conjugates without undue experimentation or burden.

In summary, the specification together with the knowledge of the art at the filing date of the application provide sufficient guidance to make the claimed conjugate for tumor imaging without any undue experimentation or burden.

Though the examiner has only rejected claims 1-16, it is noted that claims 1-19 were pending at the time of the present Office Action. The above arguments are equally applicable to the subject matter of claims 17-19 and newly added claims 20-29. As such, it is respectfully submitted that all of the presently pending claims 1-4, 7, 8, 10-15, and 18-29 are in compliance with the enablement requirement of 35 U.S.C. § 112, second paragraph. Removal of the rejection of claims 1-16 is therefore respectfully requested.

Rejection of Claims Under 35 U.S.C. §102

The Examiner has rejected claims 1, 2, 4, 5, 6, 10, 12, 15 and 16 as being anticipated under 35 U.S.C. § 102(e) by Collins et al., U.S. Patent Application Publication 2006/0074034 (hereinafter "Collins et al."). Applicants respectfully disagree.

Anticipation of a claim requires the disclosure in a single prior art reference of each element of the claim under consideration. (In re Spada, 15 USPQ2d 1655 (Fed. Cir., 1990), In re Bond, 15 USPQ2d 1566 (Fed. Cir., 1990). Collins et al. do not disclose all elements of the claimed invention.

The claimed conjugate of independent claim 1, from which dependent claims 2, 4, 5, 6, 10, 12, 15 and 16 all depend, recites a conjugate comprising the structure:

transmembrane module-address module-signalling module

In claim 1, as amended, the transmembrane module is further described as "a transport peptide capable of penetrating the plasma membrane..." (emphasis added).

By contrast, Collins et al., disclose a compound comprising vitamin B12 as carrier. Vitamin B12 is not a peptide for the transport as required by claim 1. Furthermore, vitamin B12 is a ligand of a receptor and, therefore, internalized into the cell in a different manner, i.e. by receptor-mediated endocytosis. Thus, vitamin B12 cannot be considered a compound which penetrates the plasma membrane. Hence, Collins et al. do not disclose a conjugate such as that claimed in claim 1, comprising a transmembrane module as recited therein.

As Collins et al. do not describe a conjugate as set forth in claim 1, Collins et al. do not anticipate the claimed invention of claim 1. As claims 2, 4, 5, 6, 10, 12, 15 and 16 depend from claim 1 and therefore include all elements of claim 1, Collins et al. do not anticipate the claimed invention of claims 2, 4, 5, 6, 10, 12, 15 and 16. Accordingly, withdrawal of the rejection of claims 1, 2, 4, 5, 6, 10, 12, 15 and 16 under 35 U.S.C. § 102 (e) as being anticipated by Collins et al. is respectfully requested.

Rejection of Claims Under 35 U.S.C. §103

The Examiner has rejected claims 1-7, 9, 15 and 16 as being unpatentable as obvious under 35 U.S.C. § 103 over Braun et al. (U.S. Patent No. 6,821,948; hereinafter "Braun et al.), in view of Cavaran et al., Bioconjug Chem. 1999 :361-70 (hereinafter "Cavaran et al.").

It is elemental law that in order for an invention to be obvious, the difference between the subject matter of the application and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. In order to meet this standard for a proper §103 rejection, all claim limitations must be disclosed or derivable from the cited combination of references, there must be a logical reason to combine the cited references to produce an operable combination. See MPEP §2143:

> **"2143 Basic Requirements of a Prima Facie Case of Obviousness**
>
> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

The examiner cites Braun et al. as disclosing a conjugate comprising a transport mediator of a penatrin constituent, an address protein, a Polylysine Spacer and Rhodamine and an active substance to be transported.

With regard to the address protein in Braun et al., this peptide is selected depending on the membrane to be penetrated and the target compartment of the cell to be reached (col. 3, lines 4-9). Braun et al. do not describe use of a PNA as an address module as recited in claim 1. Braun et al. provide peptides which can penetrate an intracellular membrane system or bind thereto (see col. 3, lines 33-52). However, it was known that such a PNA cannot penetrate or support penetration of a membrane system and, therefore, Braun et al. teach away from the use of such a PNA as an address module such as that recited in the claim 1.

Furthermore, the examiner asserts that the sequence of SEQ ID NO: 8 of Braun et al. has 100% homology with SEQ ID NO: 3 of the claimed invention. The SCORE results referred to by the examiner do not appear to have been provided with the Office Action mailed April 2, 2007. An examination of U.S. Patent No. 6,821,948 shows SEQ ID NO: 8 as H_3N^+-Gly-Ser-Ser-Lys-Ser-Lys-Pro-Lys. SEQ ID NO: 3 of the present application is MTRQTFWHRIKHKC. These sequences are not similar, much less identical. Clarification of the examiner's statement is respectfully requested. However, based on the information provided, it is clear that, contrary to the examiner's assertion, the address peptide of SEQ ID NO: 8 of Braun et al. is not disclosed in the present invention.

In Example 4, Braun et al. exemplify a conjugate made of a penetratin, a nucleus localization sequence (NLS), and a PNA antisense to rats P2 promoter c-myc, i.e. a promoter sequence which is not transcribed into mRNA. Hence, Braun et al. teach a PNA antisense to c-myc DNA. Braun et al. do not describe a PNA which hybridizes with a mRNA of c-myc, as alleged by the examiner.

In summary, Braun et al. does not provide any logical basis for claiming a PNA as an address module, as is recited in the claimed invention. On the contrary, Braun et al. teach that a NLS as an address peptide is additionally necessary. Therefore, Braun et al. do not provide any basis for 1) attaching the PNA directly to the transport peptide, 2) a PNA which hybridizes with a mRNA of a gene which expression or mis-expression is associated with a tumor diseases, or 3) labelling the peptide-PNA conjugate with Gadolinium.

Caravan et al. fail to overcome the deficiencies of Braun et al., and therefore the combination of references fails to provide any derivative basis for the claimed invention and, additionally, there would have been no logical reason for one of skill in the art to combine such references.

Accordingly, no basis of *prima facie* obviousness of the claimed invention is presented by such cited references.

Caravan et al. disclose the Gadolinium as an MRI contrast agent. Caravan et al. teach to prepare disease specific agents by binding Gadolinium complexes to antibodies (pages 2340 and 2341), but do not disclose binding Gadolinium to a PNA or an antisense molecule.

Hence, a skilled person would not have been motivated to combine the disclosures of Caravan et al. and Braun et al., because Caravan et al. do not provide for linking of Gadolinium to an antisense molecule and Braun et al. do not provide for use of a peptide-PNA for MRI.

However, even when combined, the skilled person would not arrive at the claimed invention from the Braun et al. and Caravan et al. references, as (i) Braun et al. disclose that a nucleus signalization sequence between the transport peptide and the PNA is required for an effective conjugate and (ii) Braun et al. do not disclose a PNA which hybridizes with a mRNA of a gene which expression or mis-expression is associated with a tumor disease.

As Braun et al. in light of Caravan et al. does not provide any logical basis for the conjugate recited in claims 1-7, 9, 15 and 16, Braun et al. in light of Caravan et al. do not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1-7, 9, 15 and 16 under 35 U.S.C. § 103 (a) as being obvious over Braun et al. in light of Caravan et al. is respectfully requested.

Fees Payable for Added Claims

By the present Amendment, 1 new independent claim and 10 new total claims have been added. Previously paid for claims were 19 total and 1 independent. The application, as amended by the present Amendment and Response, contains 2 independent claims and 22 dependent claims, for a total of 24 claims. Small entity fees payable for such added claims are calculated as follows:

$25.00 each for four (4) claims = $100.00

Payment of such fees is authorized in the enclosed Credit Card Payment Form PTO-2038.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-4, 7, 8, 10-15, and 18-29 are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

Payment of the extension fee of $60.00 specified in 37 C.F.R. § 1.17(a)(1), as applicable to small entity, is authorized by the enclosed Credit Card Payment Form PTO-2038. Payment of additional claims fees of $100.00 is also authorized by the enclosed Credit Card Payment Form PTO-2038. No additional fees are believed due in connection with the present response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

Date: August 2, 2007

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Enclosures:
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